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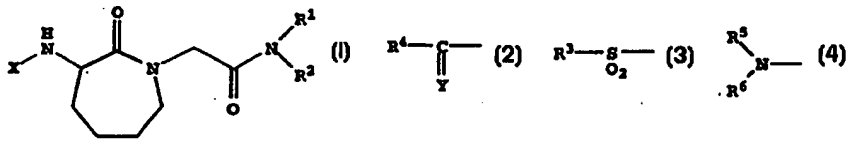

(57) Abstract

Lactam inhibitors are provided which have structure (I) wherein X is (2) or (3), Y is O or S and R^4 is (4), R^7O- or R^8, and R^1, R^2, R^3, R^5, R^6, R^7, and R^8, are as defined herein. These compounds are inhibitors of Factor Xa and thus are useful as anticoagulants. A method for treating cardiovascular diseases associated with thromboses is also provided.

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LACTAM INHIBITORS OF FXa AND METHOD

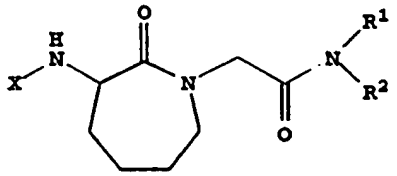
Field of the Invention

The present invention relates to lactam inhibitors of the enzyme Factor Xa which are useful as anticoagulants in the treatment of cardiovascular diseases associated with thromboses.

Brief Description of the Invention

In accordance with the present invention, novel substituted lactam derivatives are provided which are inhibitors of the enzyme Factor Xa and have the structure I

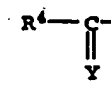
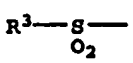
I.

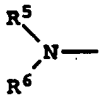


including pharmaceutically acceptable salts thereof and all stereoisomers thereof, and prodrug esters thereof, wherein

R^1 and R^2 are the same or different and are independently selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, or R^1 and R^2 can be taken with the nitrogen to which they are attached to form a cycloheteroalkyl ring; all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl,

arylaminocarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl;

X is  or 

Y is O or S and R^4 is  ,  or R^8

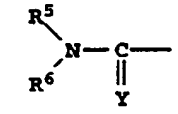
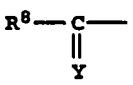
R^3 is selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, or polycycloalkenylalkyl; all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl;

R^5 and R^6 are the same or different and are independently selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, arylcarbonyl, alkylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, arylsulfonyl, or alkylsulfonyl, or R^5 and R^6 can be taken with the nitrogen to which they are attached to form a cycloheteroalkyl ring; all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl;

R^7 and R^8 are independently selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl,

cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl; with the proviso that

where in the formula I compounds

X is  or 

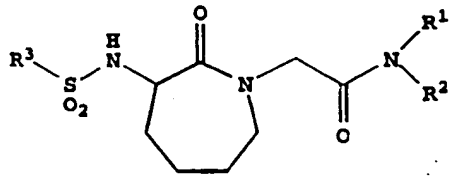
and (1) R^1 and R^2 are independently alkyl, cycloalkyl, alkenyl, phenyl, benzyl, cyanoalkyl, alkoxycarbonylalkyl, or phenyl mono- or disubstituted with lower alkyl, cyano, hydroxy, dialkylamino, alkoxy, benzyloxy, alkylamino, alkoxycarbonyl, pyrrolidino, morpholino, halogen, alkyl substituted with one or more fluorines, then Y is S;

(2) where R^1 and R^2 are alkyl, then Y is S; and

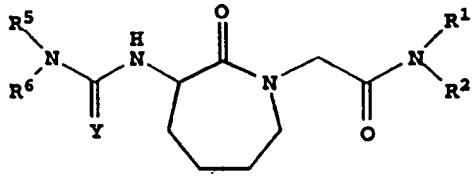
(3) where one of R^1 and R^2 is alkyl and Y is O, then the other is alkynyl, heteroaryl, heteroarylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl or R^1 and R^2 can be taken with the nitrogen to which they are attached to form a cycloheteroalkyl ring, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 substituents as defined for R^1 and R^2.

Thus, the compounds of formula I of the invention can have the following structural formulae:

IA



IB



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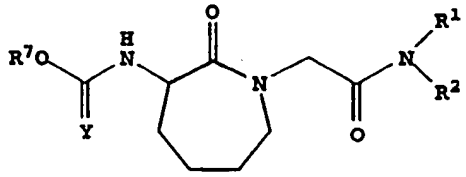

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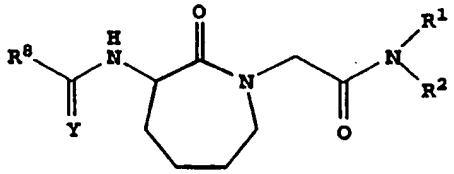


It is preferred that Y in the above formulae is S.

Preferred are compounds of formula IB wherein R^1 and R^2 together with the nitrogen to which they are attached form a cycloheteroalkyl ring, preferably a pyrrolidinyl ring, Y is S, one of R^5 and R^6 is hydrogen and the other of R^5 and R^6 is aryl, alkylaryl or alkoxyaryl such as phenyl, 3-methylphenyl or 3-methoxyphenyl, 4-cyanophenyl, 3-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 3-chloro-4-methylphenyl, 3,5-dichlorophenyl, 3-iodophenyl, 3,5-dimethylphenyl or naphthyl.

In addition, in accordance with the present invention, a method for preventing, inhibiting or treating cardovascular diseases associated with thromboses is provided, wherein a compound of formula I is administered in a therapeutically effective amount which inhibits Factor Xa.

Detailed Description of the Invention

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 40 carbons (in the case of alkyl or alk), preferably 1 to 20 carbons, more preferably 1 to 12 carbons (in the case of lower alkyl), in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various additional branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents which may be any of the R^1 or the R^1 substituents set out herein.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 4 to 12 carbons, forming the ring and which may be fused to one aromatic ring as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,

any of which groups may be optionally substituted with 1 to 4 substituents which may be any of the R^1 groups, or the R^1 substituents set out herein.

The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons

containing 5 to 20 carbons, preferably 6 to 12 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as defined for cycloalkyl.

The term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings) and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkyl-aminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfon-aminocarbonyl or any of the R^1 groups or the R^1 substituents set out herein.

The term "aralkyl", "aryl-alkyl" or "aryllower alkyl" as used herein alone or as part of another group refers to alkyl groups as discussed above having an aryl substituent, such as benzyl or phenethyl, or naphthylpropyl, or an aryl as defined above.

The term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

The term "amino" as employed herein alone or as part of another group may optionally be independently substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl or thioalkyl. These substituents may be further substituted with a carboxylic acid or any of the R^1 groups or R^1 substituents thereof as set out above. In addition, the amino substituents may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

The term "lower alkylthio", alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

The term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

The term "acyl" as employed herein by itself or part of another group, as defined herein, refers to an organic radical linked to a carbonyl $\left(\begin{matrix}O\\ \|\\ C\end{matrix}\right)$ group; examples of acyl groups include any of the R^1 groups attached to a carbonyl, such as alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl, cycloheteroalkanoyl and the like.

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 3 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonyl-amino, nitro, cyano, thiol, alkylthio or any of the R^1 groups, or the R^1 substituents set out herein.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, or any of the R^1 groups, or the R^1 substituents set out herein.

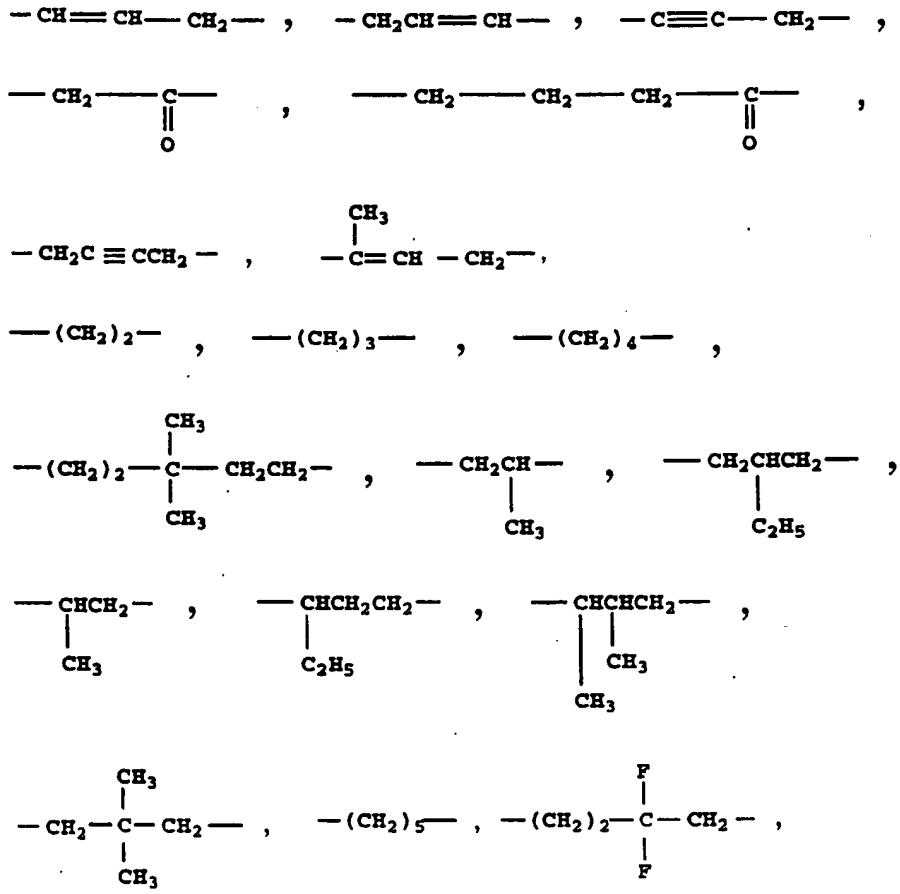
Where alkyl groups as defined above have single bonds for attachment to other groups at two different

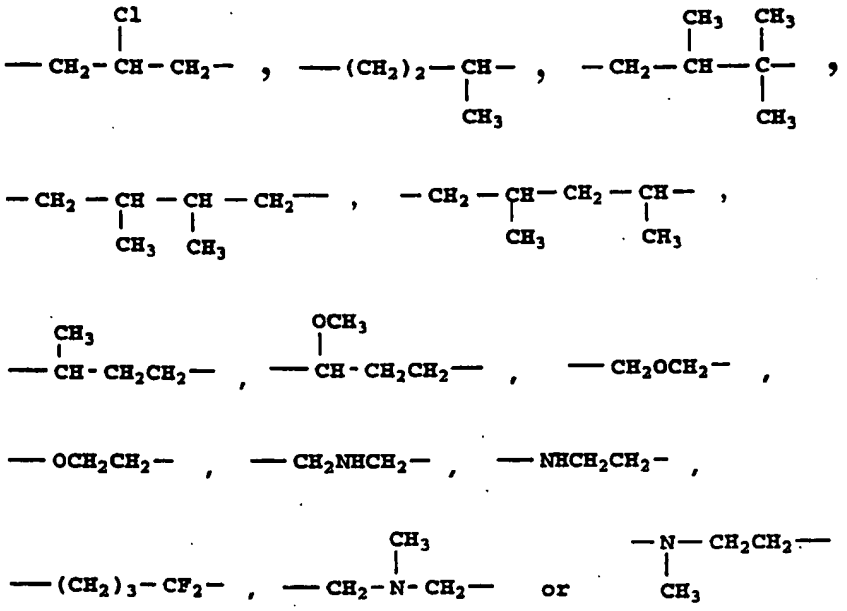
carbon atoms, they are termed "alkylene" groups and may optionally be substituted as defined above for "alkyl".

Where alkenyl groups as defined above and alkynyl groups as defined above, respectively, have single bonds for attachment at two different carbon atoms, they are termed "alkenylene groups" and "alkynylene groups", respectively, and may optionally be substituted as defined above for "alkenyl" and "alkynyl".

Suitable alkylene, alkenylene or alkynylene groups $(CH_2)_p$ (where, p is 1 to 8, preferably 1 to 5) (which may include alkylene, alkenylene or alkynylene groups) as defined herein, may optionally include 1, 2, or 3 substituents which include any of the R^1 groups, or the R^1 substituents set out herein.

Examples of alkylene, alkenylene and alkynylene include

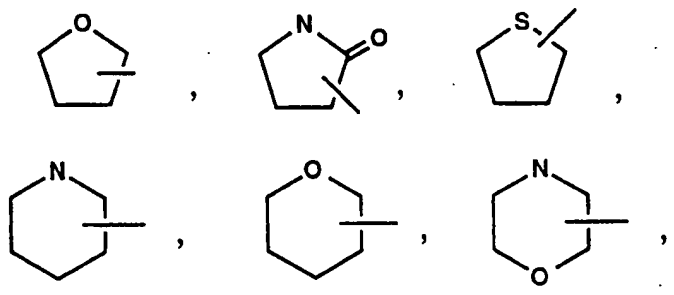


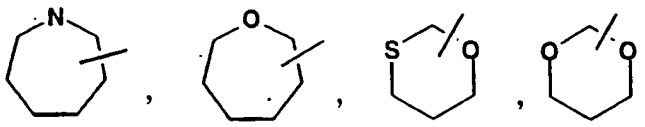


The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF_3, with chlorine or fluorine being preferred.

The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

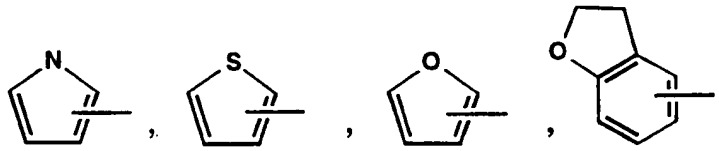
The term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (which is defined above), such as

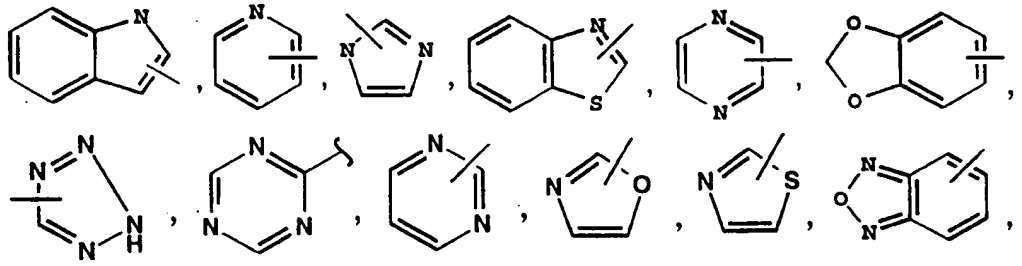


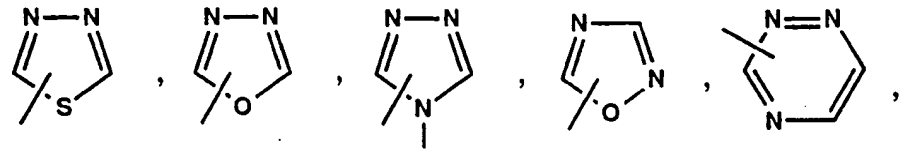


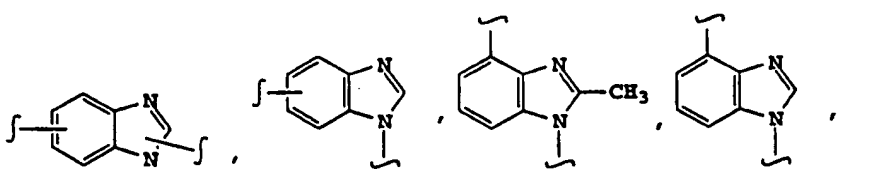
and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of of the R^1 groups, or the R^1 substituents set out herein. In addition, any of the above rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

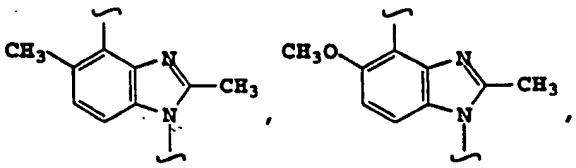
The term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur,and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), and includes possible N-oxides. The heteroaryl group may optionally include 1 to 4 substituents such as any of the R^1 groups or the R^1 substituents set out above. Examples of heteroaryl groups include the following:











and the like.

The term "cycloheteroalkylalkyl" as used herein alone or as part of another gorup refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a $(CH_2)_p$ chain.

The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a $-(CH_2)_p-$ chain, alkylene or alkenylene as defined above.

The term "polyhaloalkyl" as used herein refers to an "alkyl" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2, CF_3 or $CF_3CF_2CH_2$.

The term "polyhaloalkyloxy" as used herein refers to an "alkoxy" or "alkyloxy" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2O, CF_3O or $CF_3CF_2CH_2O$.

The compounds of formula I can be present as salts, in particular pharmaceutically acceptable salts. If the compounds of formula I have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino

acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C_1-C_4)-alkyl- or aryl-sulfonic acids which are unsubstituted or substituted, for example by halogen, for example methane- or p-toluene-sulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds of formula I having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethyl-propylamine, or a mono-, di- or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included.

Preferred salts of the compounds of formula I include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When enantiomeric or diastereomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

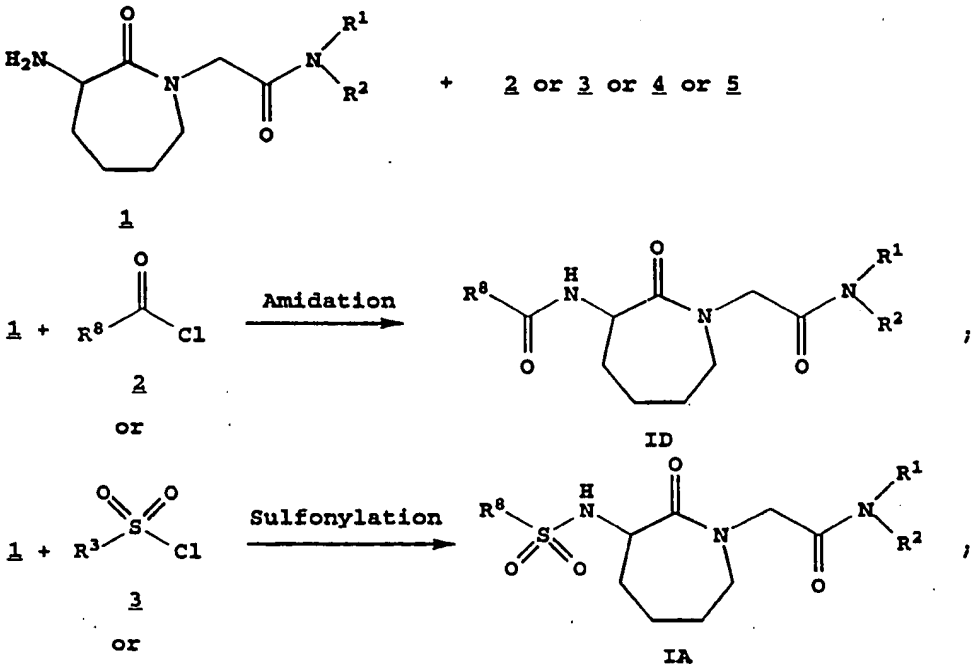
It should be understood that the present invention includes prodrug forms of the compounds of formula I such as alkylesters of acids or any known prodrugs for lactam derivatives.

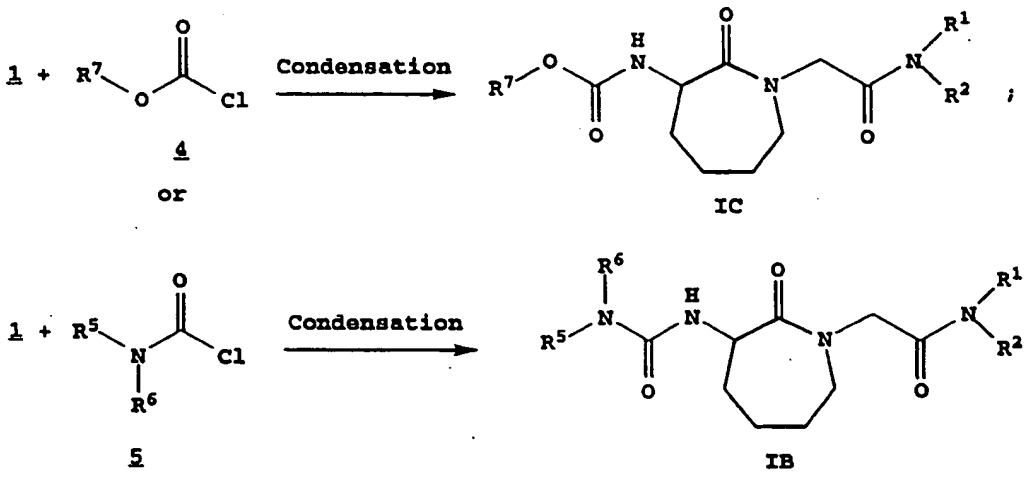
The compounds of the instant invention may, for example, be in the free or hydrate form, and may be obtained by methods exemplified by the following descriptions.

The compounds of formula I may be prepared by the exemplary processes described in the following reaction schemes. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples.

Compounds of formula I of the invention can be prepared from the corresponding amine 1 by using the sequence of steps outlined in Scheme I set out below.

Reaction Scheme I

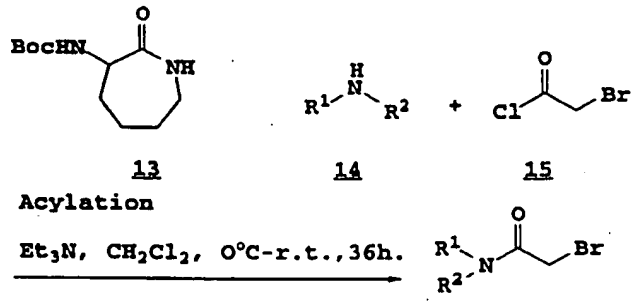


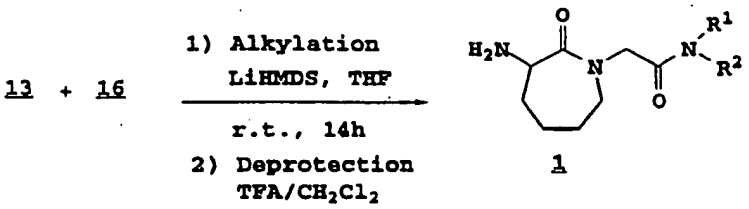


Reaction of amine 1 in an inert organic solvent such as dichloromethane, chloroform or tetrahydrofuran with reactant acid chloride 2, sulfonyl chloride 3, chloroformate 4 or carbamoylchloride 5, employing a molar ratio of reactant:amine 1 within the range from about 5:1 to about 1:5, optionally in the presence of an acid scavenger such as triethylamine, diisopropylethylamine, pyridine, or polyvinylpyridine, forms compounds ID, IA, IC or IB of the invention.

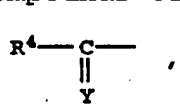
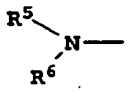
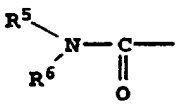
Starting compound 1 can be prepared by methods known in the art as outlined in Reaction Scheme IA below.

Reaction Scheme IA



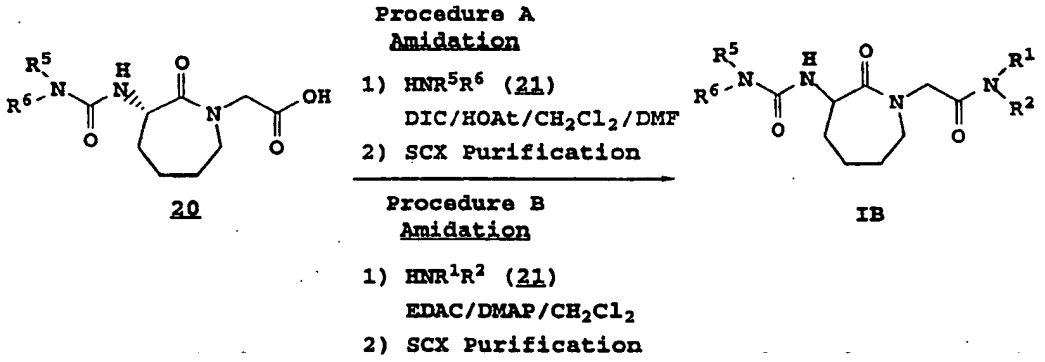


Compound 1 is a novel compound provided that R^1 and R^2 are as defined herein, but excludes alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or polycycloalkyl.

Compounds of formula I of the invention wherein X is  , Y is O and R^4 is  , that is 

can be prepared from the corresponding acid 6 by using the sequence of steps outlined in Scheme II (Procedures A and B) set out below.

Reaction Scheme II



Procedure A: For amines where R^1 and/or R^2 contain additional basic nitrogens.

Procedure B: For amines where R^1 and/or R^2 contain no additional basic nitrogens.

In Procedure A (for amines where R^1 and/or R^2 contain additional basic nitrogens), a mixture of a solution of

amine 21 in an inert organic solvent such as THF, methylenechloride or chloroform, a carbodiimide such as diisopropylcarbodiimide (DIC) and 7-aza-1-hydroxy-benzotriazole (HOAt) is reacted with acid 20, employing a molar ratio of amine 21:acid 20 within the range from about 5:1 to about 1:5, preferably at about 1:1.1, to form a reaction mixture which is purified via an SCX column to separate out compound IB of the invention.

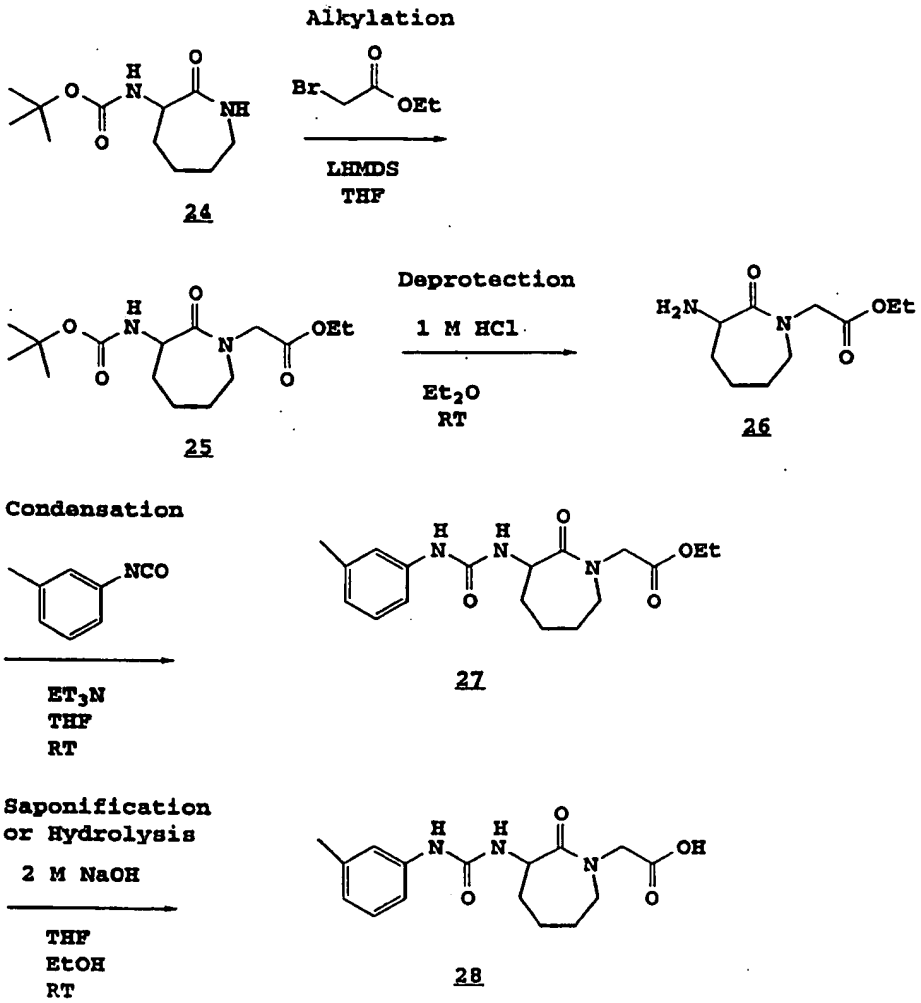
The DIC will be employed in a molar ratio to acid 20 within the range from about 5:1 to about 1:5, preferably at about 1.6:1, and the HOAt will be employed in a molar ratio acid 20 within the range from about 5:1 to about 1:5, preferably at about 1.6:1.

In Procedure B (for amines where R^1 and/or R^2 contain no additional basic nitrogens) a mixture of a solution of amine 21 in an inert organic solvent such as THF , methylenechloride or chloroform, ethyldimethylaminopropylcarbodiimide (EDAC) and dimethylaminopyridine (DMAP) with acid 20, employing a molar ratio of amine 21:acid 20 within the range from about 5:1 to about 1:5, preferably at about 1.5:1, to form a reaction mixture which is purified via a SCX column to separate out compound IB of the invention.

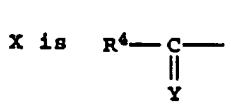
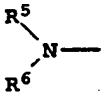
The EDAC will be employed in a molar ratio to acid 20 within the range from about 5:1 to about 1.5, preferably at about 1.5:1, and the DMAP will be employed in a molar ratio to acid 20 within the range from about 5:1 to about 1:5, preferably at about 1.5:1.

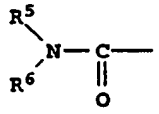
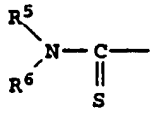
Starting compound 20 can be prepared by methods known in the art as outlined in Reaction Scheme IIA.

Reaction Scheme IIA



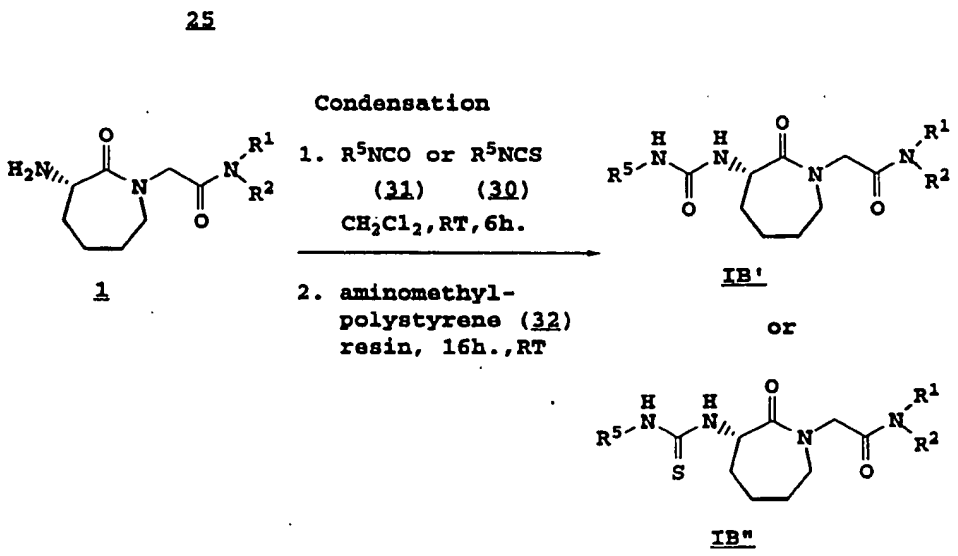
Compounds of formula I of the invention wherein

X is  , Y is O or S, and R^4 is  ,

that is  or 

can be prepared from the corresponding amine 1 by using the sequence of steps outlined in Scheme III set out below.

Reaction Scheme III



Reaction of amine 1 (in an inert organic solvent such as dichloromethane, chloroform or tetrahydrofuran) with reactant 30 or 31 employing a molar ratio of 30 or 31:amine 1 within the range of from about 5:1 to about 1:5, followed by treatment with aminomethylpolystyrene (32), affords the compound of the invention IB' or IB".

The compounds of the present invention are inhibitors of the activated coagulation serine protease known as Factor Xa and thus are useful for the treatment or prophylaxis of those processes which involve the production and/or action of Factor Xa. Thus, the compounds of the invention are useful in the treatment or prevention of thrombotic events associated with coronary artery and cerebrovascular disease. This includes a number of thrombotic and prothrombotic states in which the coagulation cascade is activated which include, but are not limited to, formation of atherosclerotic plaques, venous or arterial thrombosis, coagulation syndromes, ischemia and angina (stable and unstable), deep vein thrombosis (DVT), disseminated intravascular coagulopathy, Kasabach-Merritt syndrome, pulmonary embolism, myocardial infarction, cerebral infarction, cerebral thrombosis, atrial

fibrillation, cerebral embolism, thromboembolic complications of surgery (such as hip replacement, introduction of artificial heart valves and endarterectomy) and peripheral arterial occlusion. The compounds of the invention are also useful as inhibitors of blood coagulation such as during the preparation, storage and fractionation of whole blood.

The present compounds may also be useful in maintaining whole and fractionated blood in the fluid phase such as required for analytical and biological testing. Examples include, but are not limited to, ex vivo platelet and other cell function studies, bioanalytical procedures and quantitation of blood-containing components.

In addition, the compounds of the present invention may be useful to prevent restenosis following arterial injury induced by endogenous (rupture of an atherosclerotic plaque) or exogenous (invasive cardiological procedure such as vessel wall injury resulting from angioplasty) events.

The compounds of the present invention may also be used as an anticoagulant in extracorpeal blood circuits, such as those necessary in dialysis and surgery (such as coronary artery bypass surgery).

In addition, the compounds of the present invention may be useful for maintaining blood vessel patency in conjunction with vascular surgery including bypass grafting, arterial reconstruction, atherectomy, vascular graft and stent patency, organ, tissue and cell implantation and transplantation.

The compounds of the present invention may be useful for the treatment of heparin-intolerant patients, including those with congenital and acquired antithrombin III deficiencies, heparin-induced thrombocytopenia, and those with high levels of polymorphonuclear granulocyte elastase.

The compounds of the present invention may also be useful for the treatment of inflammatory diseases and the prevention of septic shock and vascular damage due to bacterial and/or viral infections.

The compounds of the present invention may also be useful in the treatment of malignancies, prevention of metastases, prevention of prothrombotic complications of cancer, and as an adjunct to chemotherapy.

The compounds of the present invention may also be used in combination with prothrombolytic agents, such as tissue plasminogen activator (natural or recombinant), streptokinase, reteplase, activase, lanoteplase, urokinase, prourokinase, anisolated streptokinase plasminogen activator complex (ASPAC), animal salivary gland plasminogen activators, and the like. The compounds of the present invention may act in a synergistic fashion with one or more of the above agents to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. The compounds of the present invention may also allow for reduced doses of the thrombolytic agent to be used and therefore minimize potential hemorrhagic side-effects.

The compounds of the present invention may also inhibit other serine proteases, for example, thrombin, Factor VIIa, urokinase-type plasminogen activator (urokinase), tryptase and/or trypsin. As a result, these compounds may additionally be useful as angiogenesis inhibitors in the treatment of cancer, as antiinflammatory agents particularly in the treatment of chronic asthma and in the treatment or prevention of allergic rhinitis, rheumatoid arthritis, inflammatory bowel disease, psoriasis, and conjunctivitis and in the treatment or prevention of pancreatitis.

The compounds of the present invention may also be used in combination with other antithrombotic or anticoagulant drugs such as thrombin inhibitors, platelet aggregation inhibitors such as clopidogrel, ticlopidine, PAI-1 inhibitors such as XR-330 and T-686, inhibitors of α-2-antiplasmin such as anti-α-2-antiplasmin antibody and thromboxane receptor antagonists (such as ifetroban), prostacyclin mimetics, phosphodiesterase (PDE) inhibitors,

such as dipyridamole or cilostazol, PDE inhibitors in combination with thromboxane receptor antagonists/thromboxane A synthetase inhibitors (such as picotamide), serotonin-2-receptor antagonists (such as ketanserin), fibrinogen receptor antagonists, aspirin, hypolipidemic agents, (such as HMG-CoA reductase inhibitors for example pravastatin or simvastatin, or microsomal triglyceride transport protein inhibitors such as disclosed in U.S. Patent Nos. 5,739,135, 5,712,279 and 5,760,246), antihypertensive agents, (such as angiotensin converting enzyme inhibitors, for example, captopril, lisinopril or fosinopril, angiotensin II receptor antagonists, for example, irbesartan, losartan or valsartan, and ACE/NEP inhibitors, for example omapatrilat), PDE inhibitors in combination with aspirin, ifetroban, picotamide, ketanserin or clopidogrel and the like.

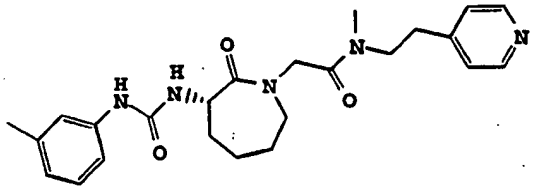
The compounds of the invention can be administered orally or parenterally such as subcutaneously or intravenously, as well as by nasal application, rectally or sublingually to various mammalian species known to be subject to such maladies, e.g., humans, cats, dogs and the like in an effective amount within the dosage range of about 0.1 to about 100 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg (or from about 1 to about 2500 mg, preferably from about 5 to about 2000 mg) on a regimen in single or 2 to 4 divided daily doses.

The active substance can be utilized in a composition such as tablet, capsule, solution or suspension or in other type carrier materials such as transdermal devices, iontophoretic devices, rectal suppositories, inhalant devices and the like. The composition or carrier will contain about 5 to about 500 mg per unit of dosage of a compound or mixture of compounds of formulas I, IA., IB, IC and ID. They may be compounded in conventional matter with a physiologically acceptable vehicle or carrier,

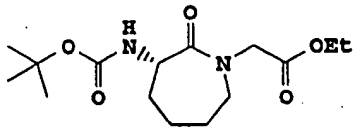
excipient, binder, preservative, stabilizer, flavor, etc., as called for by accepted pharmaceutical practice.

The following working Examples represent preferred embodiments of the present invention.

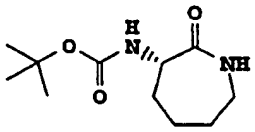
Example 1



A.

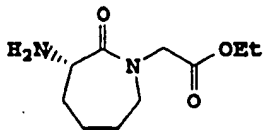


To a solution of 8.3 g (36 mmol, 1 eq) of



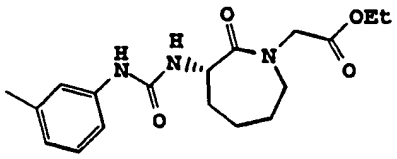
compound in 40 mL of dry THF was added dropwise 72 mL (72 mmol, 2 eq) of a 1 M solution of lithium hexamethyldisilazide (LHMDS) in THF over 1 h. After 10 min, a solution of 4.4 mL (40 mmol, 1.1 eq) of bromoethylacetate in 10 mL of dry THF was added dropwise over 10 min and the resulting reaction mixture was stirred at RT for 17 h. The reaction mixture was diluted with diethyl ether (100 mL) and washed twice with 5% $KHSO_4$ (aq.), followed by saturated $NaHCO_3$ and brine. The organic solution was dried ($MgSO_4$) and concentrated to afford 11.3 g (99%) of title compound as a viscous yellow brown oil. 1H and 13C NMR spectra were consistent with the desired product and indicated the material was pure except for a small amount of hexamethyldisilazane. The material was used without further purification.

B.



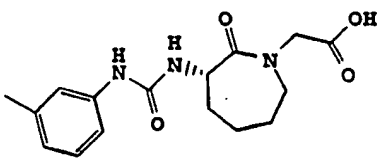
To a solution of 7.8 g (25 mmol, 1 eq) of Part A compound in 10 mL of diethyl ether was added 50 mL (50 mmol, 2 eq) of a 1 M solution of hydrochloric acid in diethyl ether. The reaction mixture was stirred at RT for 18 h. The resulting heterogeneous reaction mixture was concentrated and the oily residue was triturated with ether, dissolved in methanol and concentrated to afford 5.1 g (81%) of title compound as a yellow solid. 1H and 13C NMR spectra were consistent with the desired product.

C.



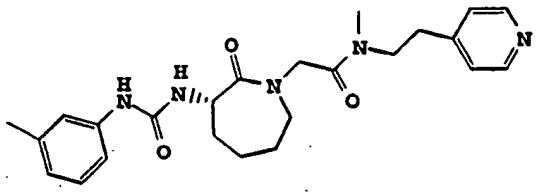
To a solution of 5.1 g (20 mmol, 1 eq) of Part B compound in 120 mL of dry THF was added 5.7 mL (41 mmol, 3 eq) of triethylamine and 3.9 mL (30 mmol, 1.5 eq) of m-tolylisocyanate. The reaction mixture was stirred at RT for 18 h. The reaction mixture was concentrated and the residue dissolved in methnol. An insoluble impurity was removed by filtration and the crude product was again concentrated. Flash chromatography (SiO_2) eluting with 9:1 CH_2Cl_2:ethyl acetate (EtOAc) afforded 3.3 g (48%) of title compound as a light brown solid. 1H and 13C NMR spectra were consistent with the desired product.

D.



To a solution of 2.3 g (7 mmol, 1 eq) of Part C compound in 30 mL of THF and 30 mL of EtOH was added 8.3 mL (17 mmol, 2.5 eq) of 2 M sodium hydroxide in water. The reaction mixture was stirred at RT for 18 h. The reaction mixture was concentrated, the residue was dissolved in 20 mL of water and the pH was adjusted to 3 with 1 M HCl. The resulting precipitate was collected by filtration, washed with water (10 mL), washed with hexane (10 mL) and dried to afford 1.7 g (82%) of title compound as a light yellow solid. 1H and 13C NMR spectra were consistent with the desired product.

E.



The title compound was prepared as part of an automated solution phase run using a liquid handler (Hamilton Microlab® 2200) for reagent and starting material addition using the following procedure.

To a 16 mm x 100 mm reaction tube was added via the liquid handler 100 µL (3.9 mg, 0.036 mmol, 1 eq) of a stock solution of 4-[2-(methylamino)ethyl]pyridine in THF, 300 µL (7 mg, 0.057 mmol, 1.6 eq) of a stock solution of diisopropylcarbodiimide in CH_2Cl_2, 300 µL (8 mg, 0.057 mmol, 1.6 eq) of a stock solution of 7-aza-1-hydroxy-benzotriazole in DMF and 300 µL (12 mg, 0.038 mmol, 1.05 eq) of a stock solution of Part D compound in CH_2Cl_2. The tube was removed and mixed on an orbital shaker for 72 h.

The product was purified via solid phase extraction using a Varian SCX cation exchange column (1 g of sorbent in 6 mL column, 0.3 meq/g) by the procedure outlined below:

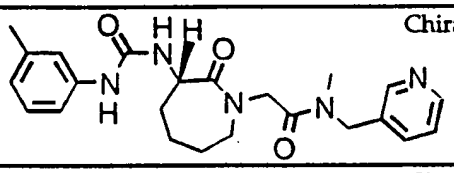
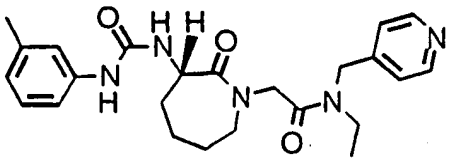
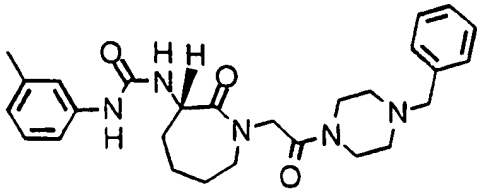
1) Column conditioned with 2 x 7.5 mL of MeOH (10 mL/min).
2) Reaction mixture (1 mL) loaded onto SCX column (3 mL/min).
3) Column rinsed with 20 mL of MeOH (6 mL/min).
4) Column rinsed with 10 mL of 0.1 N ammonia in MeOH (6 mL/min).
5) Product eluted with 8 mL of 2 N ammonia in MeOH into a tared 16 x 100 tube (6 mL/min).

The product solution was concentrated using a speed vac for 14 h to afford 17 mg of title compound (109%) as an oil. Reverse phase analytical HPLC analysis indicated a purity of 96%.

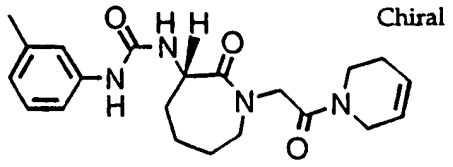
MS (electrospray): m/z 438 (M+H).

Examples 2 to 4

Following the procedure of Example 1, the following compounds of the invention were prepared.

Example No.	Structure	Mass Spec. m/z $(M+H)^+$
2	 Chiral	424
3	 Chiral	438
4	 Chiral	479

Example 5



Example 5 was prepared as part of an automated solution phase run using a liquid handler (Hamilton Microlab® 2200) for reagent and starting material addition using the following procedure.

To a 16 mm x 100 mm reaction tube was added via the liquid handler 100 µL (0.057 mmol, 1.5 eq) of a stock solution of 1,2,3,6-tetrahydropyridine in THF, 300 µL of a stock solution containing both ethyldimethylaminopropyl-carbodiimide hydrochloride (0.057 mmol, 1.5 eq) and dimethylaminopyridine (0.057 mmol, 1.5 eq) in CH_2Cl_2 and 600 µL (0.038 mmol, 1.0 eq) of a stock solution of Example 1 Part D compound in CH_2Cl_2. The tube was removed and mixed on an orbital shaker for 72 h.

The product was purified via solid phase extraction using a Varian SCX cation exchange column (1 g of sorbent in 6 mL column, 0.3 meq/g) by the procedure outlined below.

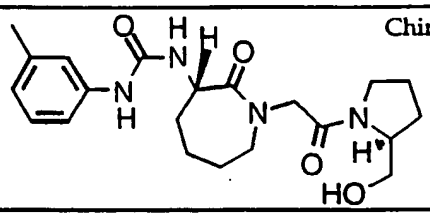
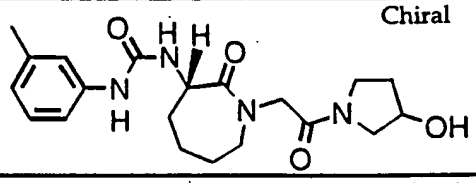
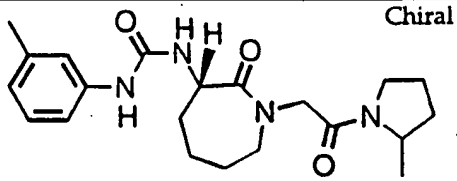
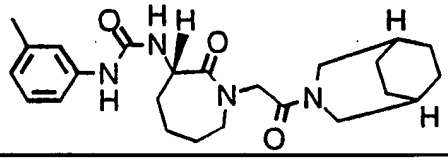
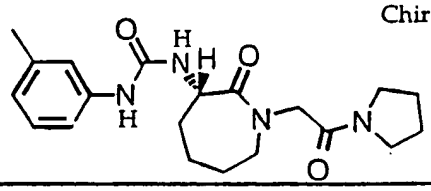
1) Column conditioned with 15 of MeOH (10 mL/min).
2) Reaction mixture (1 mL) was loaded onto SCX column (3 mL/min) and effluent was collected into a tared 16 mm x 100 mm tube.
3) Column rinsed with 6 mL of MeOH and collected into tared tube (6 mL/min).

The product solution was concentrated using a speed vac for 14 h to afford 14 mg of Example 5 compound (94%) as an oil. Reverse phase analytical HPLC analysis indicated a purity of 97%.

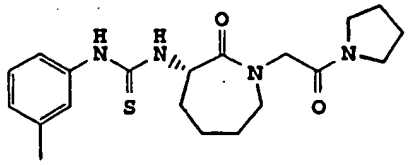
MS (electrospray): m/z 385 (M + H).

Example 6 to 10

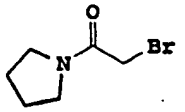
Following the procedure of Example 5, the following compounds of the invention were prepared.

Example No.	Structure	Mass Spec. m/z $(M+H)^+$
6	 Chiral	403
7	 Chiral	389
8	 Chiral	387
9	 Chiral	427
10	 Chiral	373

Example 11

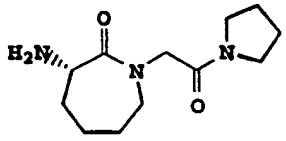


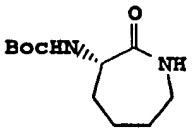
A.



To a solution of $Cl-\overset{O}{\overset{\|}{C}}-CH_2-Br$ (55 g, 0.35 mol) in 400 mL of CH_2Cl_2 was added dropwise a solution of pyrrolidine (25 g, 0.35 mol) and triethylamine (42.4 g, 0.42 mol) in 100 mL of CH_2Cl_2 at 0°C under argon over 5h. The reaction mixture was allowed to slowly warm to room temperature with stirring for an additional 14h. The reaction mixture was washed with H_2O (250 mLx3), 0.5 N HCl (250 mL), saturated NaCl (300 mLx3), and dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash column chromatography (elute with 1% MeOH in CH_2Cl_2) to yield title compound (46.1 g, 68.6%) as off-brown solid. Found: MH^+: 191.7.

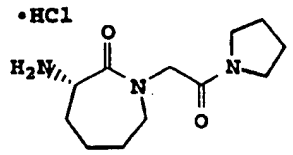
B.





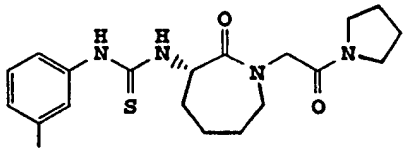
To a solution of (8.0 g, 35.1 mmol) in 600 mL of THF was added dropwise 70.2 mL of LHMDS (1.0 M in THF) at room temperature under argon over 3h, followed by adding dropwise a solution of Part B compound (7.4 g, 38.6 mmol) in 100 mL of THF over 2h. The reaction mixture was stirred for an additional 14h at room temperature. The reaction mixture was poured into 5% $KHSO_4$ (300 mL), and added ethylacetate (AcOEt) (300 mL). The organic layer was washed with 5% $KHSO_4$ (300 mL), saturated $NaHCO_3$ (300 mLx2), H_2O (300 mLx3), and dried (Na_2SO_4) and concentrated to yield title compound (11.1 g, 93.2%) as yellow oil. Found: MH^+: 340.1.

C.



To a solution of Part B compound (4.1 g, 12.1 mmol) in 100 mL of CH_2Cl_2 was added 100 mL of HCl in Et_2O (1.0 M) at room temperature. The mixture was stirred for 14h. The solvent was removed in vacuum and the resulting residue was purified by ion-exchange resin column chromatography (elute with 2% ammonia in MeOH) to yield title compound (1.91 g, 66.0%) as yellow oil. Found: MH^+: 240.2.

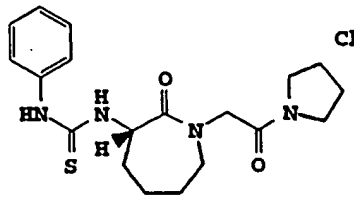
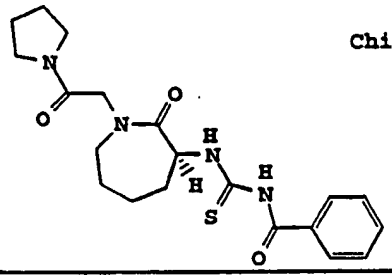
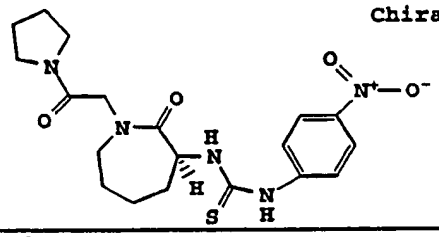
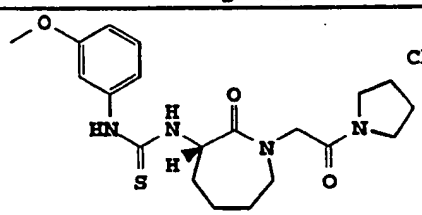
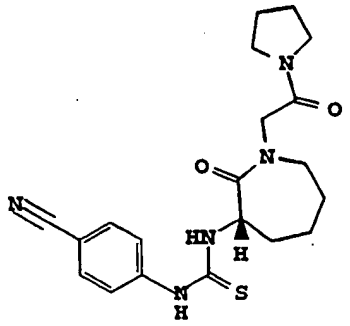
D.



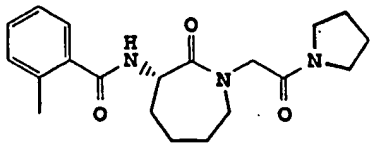
To a solution of Part C compound (90.8 mg, 0.38 mmol) in 3 mL of CH_2Cl_2 was added a solution of m-tolyl-isothiocyanate (51.5 mg, 0.345 mmol) in 2 mL of CH_2Cl_2 at room temperature. The reaction mixture was stirred for 0.5h and concentrated in vacuum. The resulting residue was purified by flash column chromatography (eluted with 1% MeOH in CH_2Cl_2) to yield title compound (130 mg, 97.0%) as white solid. Found: MH^+: 389.1.

Examples 12 to 16

The following compounds of the invention were prepared employing procedures described in Example 11.

Example No.	Structure	Mass Spec. m/z $(M+H)^+$
12	 Chiral	375
13	 Chiral	403
14	 Chiral	420
15	 Chiral	405
16	 Chiral	400

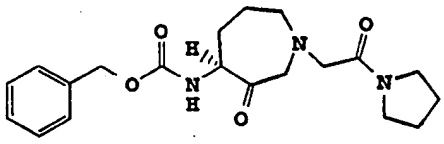
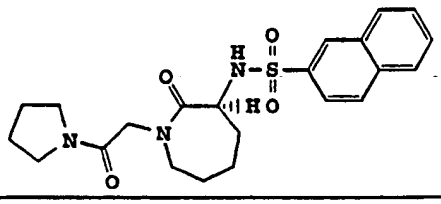
Example 17



To 13.9 mg of polyvinylpyridine (9.0 mmol/g) was added 0.400 mL of solution of Example 13, Part C compound in dichloromethane (0.158 mmol/mL) and 0.400 mL of solution of o-toluoyl chloride in dichloromethane (0.173 mmol/mL). The mixture was shaken for 4h. at room temperature. The reaction mixture was then added to 31.4 mg of aminomethylpolystyrene (1.0 mmol/g) and 0.200 mL of dichloromethane. The mixture was shaken for 14h at room temperature. The reaction solution was collected and the residue resins were washed with dichloromethane (0.400 mL). The combined reaction solutions were dried by speed vacuum to yield title compound (17.1 mg, 69%). Found: MH^+: 358.1.

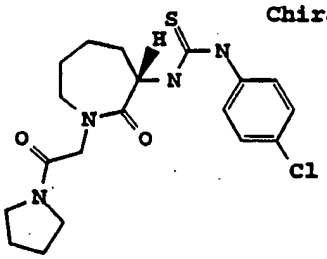
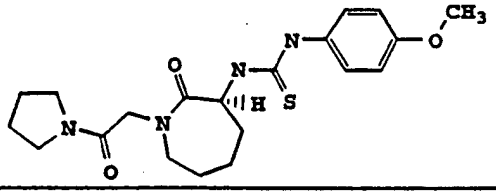
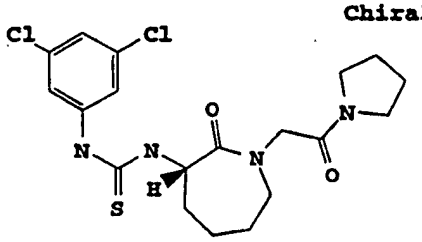
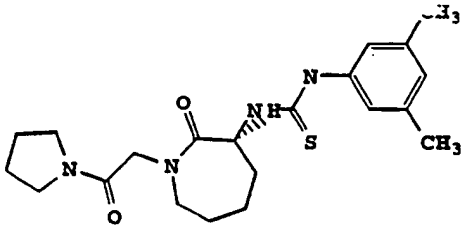
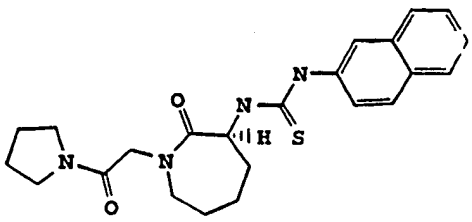
Examples 18, 19

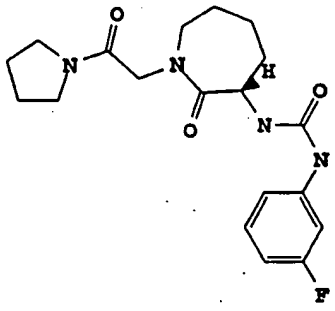
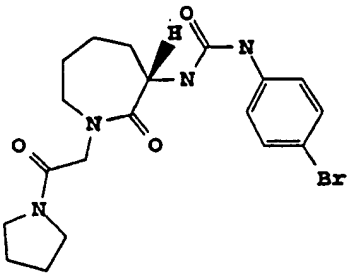
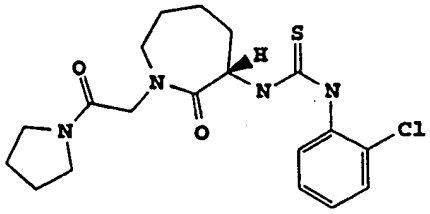
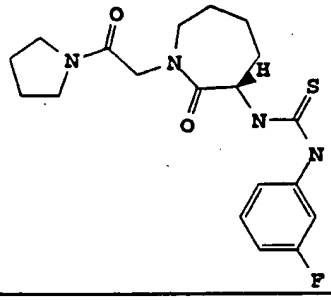
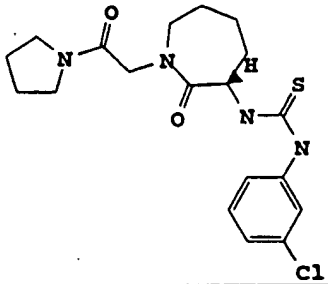
The following compounds were prepared employing the procedure as described in Example 17.

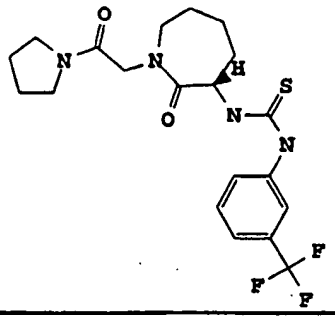
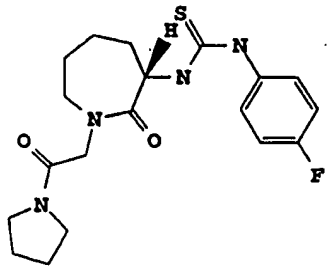
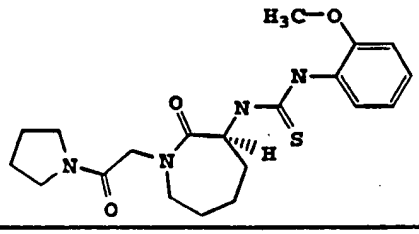
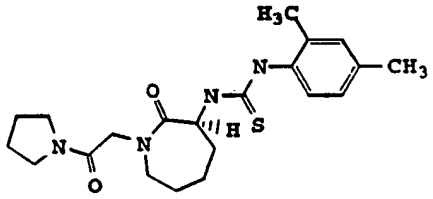
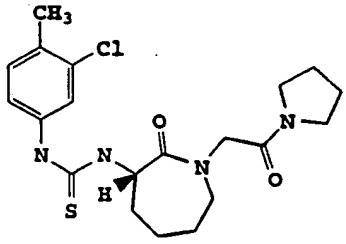
Example No.	Structure	Mass Spec.
18	Chiral 	374
19	Chiral 	430

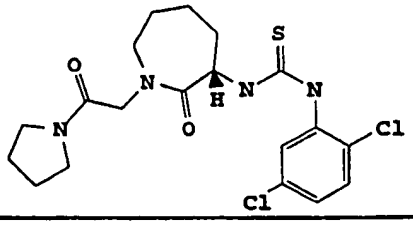
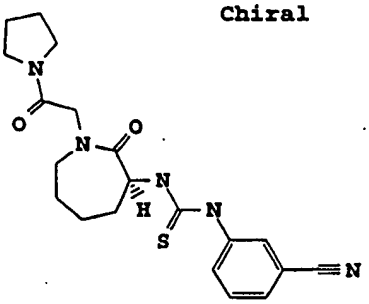
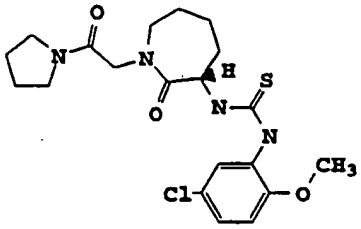
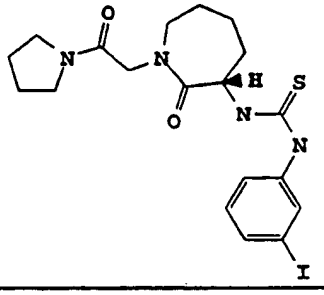
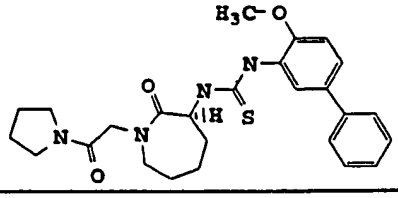
Examples 20 to 57

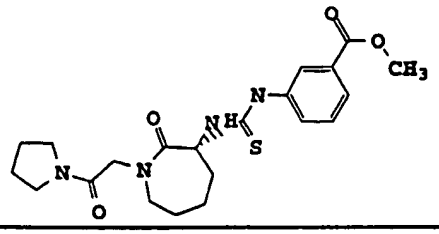
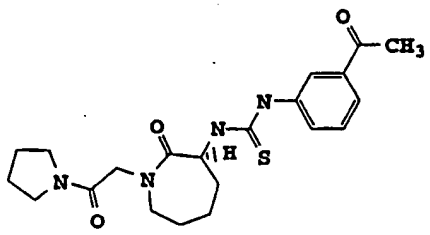
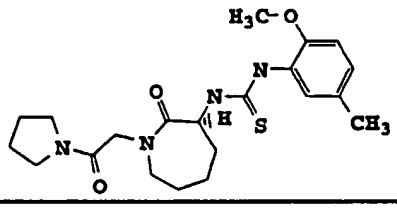
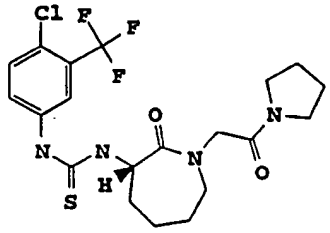
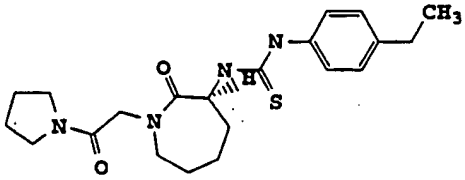
The following compounds were prepared employing procedures as described in previous Examples.

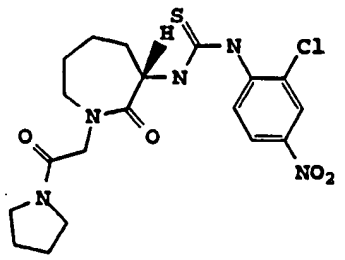
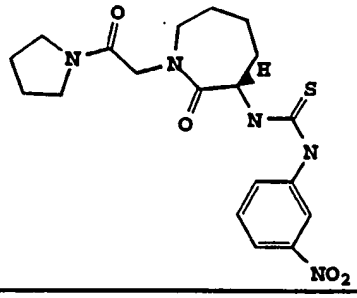
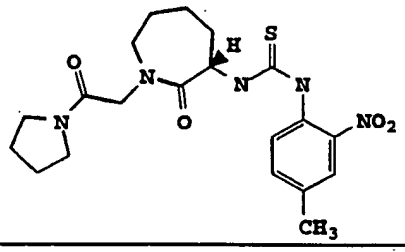
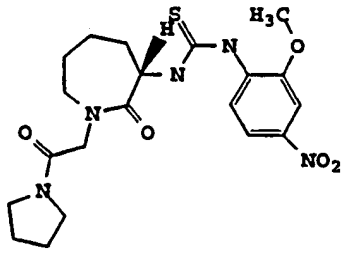
Example No.	Structure	Mass Spec. m/z $(M+H)^+$
20	 Chiral	409
21	Chiral 	405
22	Chiral 	443
23	Chiral 	403
24	Chiral 	425

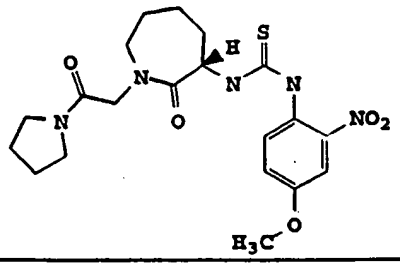
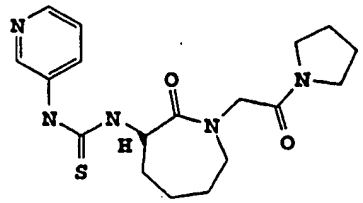
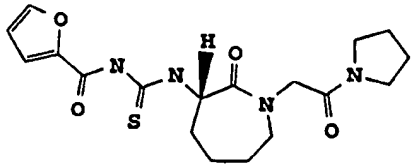
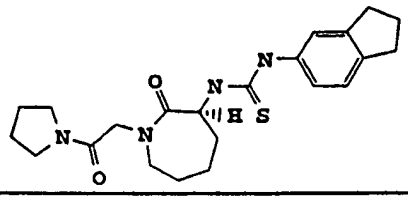
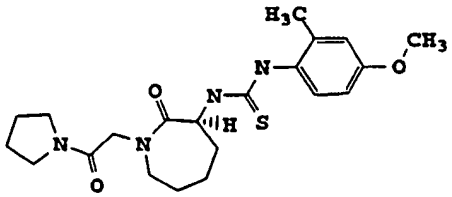
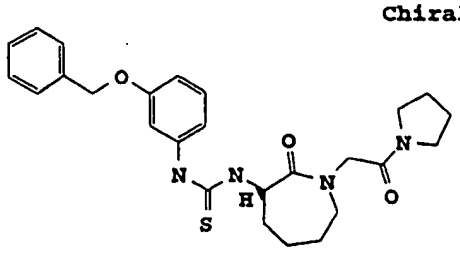
25	Chiral 	377
26	Chiral 	437
27	Chiral 	409
28	Chiral 	393
29	Chiral 	409

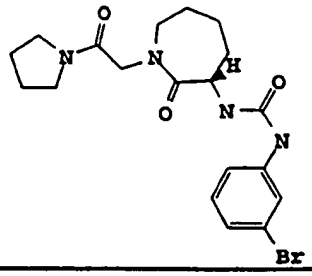
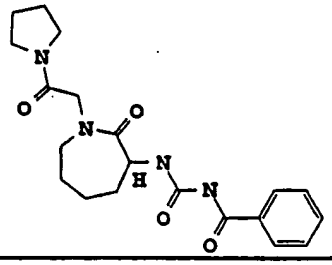
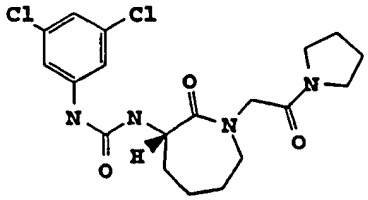
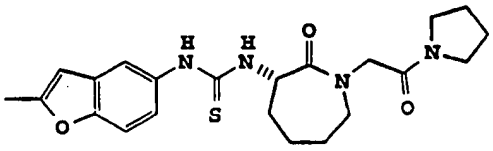
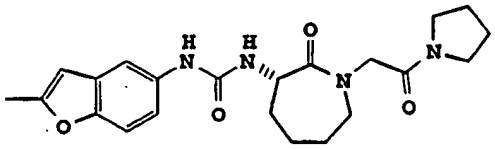
30	Chiral 	443
31	Chiral 	393
32	Chiral 	405
33	Chiral 	403
34	Chiral 	423

35	Chiral 	443
36	Chiral 	400
37	Chiral 	439
38	Chiral 	501
39	Chiral 	481

40	Chiral 	433
41	Chiral 	417
42	Chiral 	419
43	Chiral 	477
44	Chiral 	403

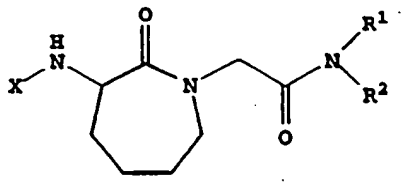
45	Chiral 	454
46	Chiral 	420
47	Chiral 	434
48	Chiral 	450

49	Chiral 	450
50	Chiral 	376
51	Chiral 	393
52	Chiral 	415
53	Chiral 	419
54	Chiral 	481

55	Chiral 	437
56	Chiral 	387
57	Chiral 	427
58	Chiral 	429
59	Chiral 	413

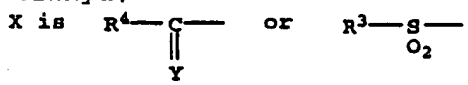
What is Claimed is:

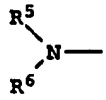
1. A compound having the formula



including pharmaceutically acceptable salts thereof and all stereoisomers thereof, and prodrug esters thereof, wherein

R^1 and R^2 are the same or different and are independently selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, or polycycloalkenylalkyl, or R^1 and R^2 can be taken with the nitrogen to which they are attached to form a cycloheteroalkyl ring; all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheterolkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl;

X is  or

Y is O or S and R^4 is  , R^7O— or R^8

R^3 is selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, or polycycloalkenylalkyl; all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl,

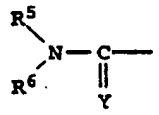
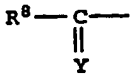
R^5 and R^6 are the same or different and are independently selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, arylcarbonyl, alkylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, arylsulfonyl, or alkylsulfonyl, or R^5 and R^6 can be taken with the nitrogen to which they are attached to form a cycloheteroalkyl ring; all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy,

alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl;

R^7 and R^8 are independently selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl,

arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl;

with the proviso that where

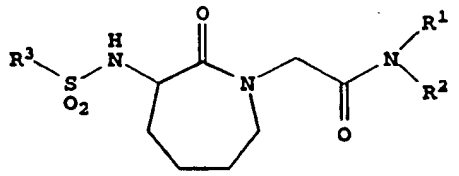
X is  or 

and (1) R^1 and R^2 are independently cycloalkyl, alkenyl, phenyl, benzyl, cyanoalkyl, alkoxycarbonylalkyl, or phenyl mono- or disubstituted with lower alkyl, cyano, hydroxy, dialkylamino, alkoxy, benzyloxy, alkylamino, alkoxycarbonyl, pyrrolidino, morpholino, halogen, alkyl substituted with one or more fluorines, then Y is S;

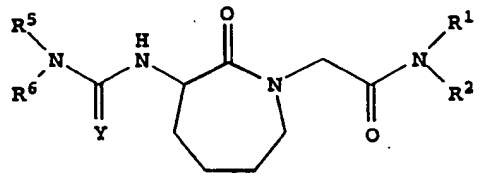
(2) where R^1 and R^2 are alkyl, then Y is S; and

(3) where one of R^1 and R^2 is alkyl and Y is O, then the other is alkynyl, heteroaryl, heteroarylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl or R^1 and R^2 can be taken with the nitrogen to which they are attached to form a cycloheteroalkyl ring, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 substituents as defined for R^1 and R^2.

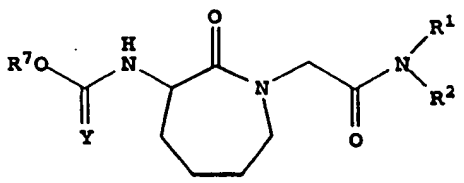
2. The compound as defined in Claim 1 having the formula



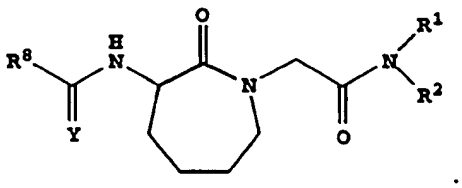
3. The compound as defined in Claim 1 having the formula

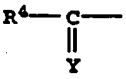


4. The compound as defined in Claim 1 having the formula



5. The compound as defined in Claim 1 having the formula



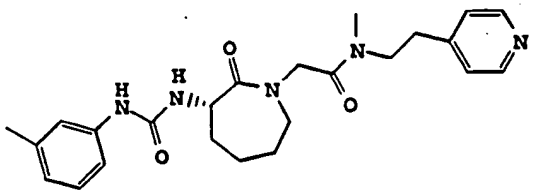
6. The compound as defined in Claim 1 wherein X is  and Y is S.

7. The compound as defined in Claim 3 wherein Y is S.

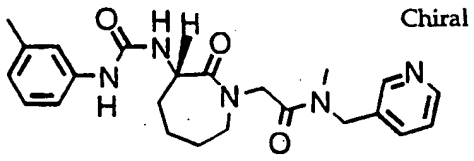
8. The compound as defined in Claim 3 wherein R^1 and R^2 together with the nitrogen to which they are attached form a cycloheteroalkyl ring, Y is S, one of R^5 and R^6 is hydrogen and the other of R^5 and R^6 is aryl, alkylaryl or alkoxyaryl.

9. The compound as defined in Claim 8 wherein R^1 and R^2 together with the nitrogen to which they are attached form a pyrrolidinyl ring, Y is S, one of R^5 and R^6 is hydrogen and the other of R^5 and R^6 is phenyl, 3-methylphenyl, 3-methoxyphenyl, 4-cyanophenyl, 3-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 3-chloro-4-methylphenyl, 3,5-dichlorophenyl, 3-iodophenyl, 3,5-dimethylphenyl or naphthyl.

10. The compound as defined in Claim 1 having the structure



Chiral



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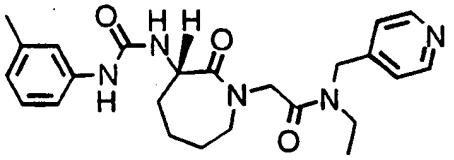

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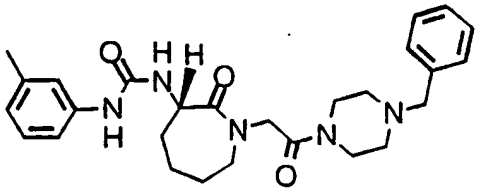

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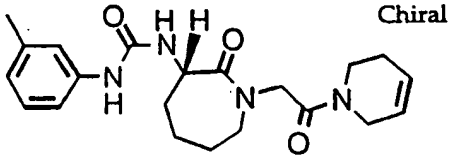

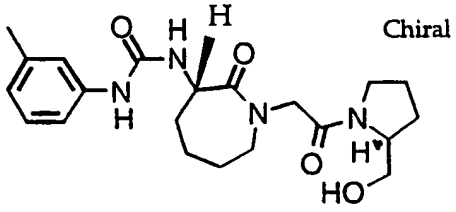

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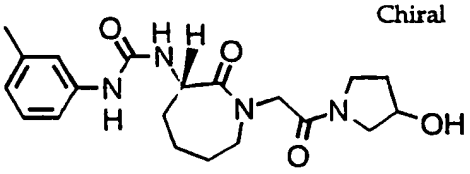

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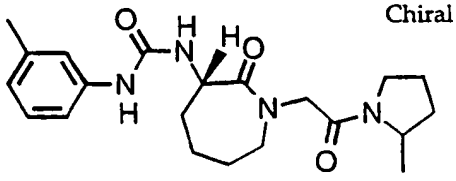

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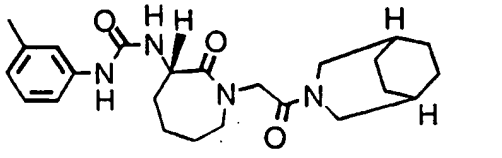

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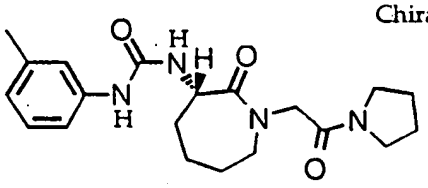

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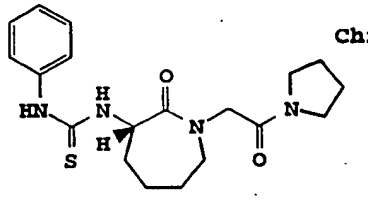

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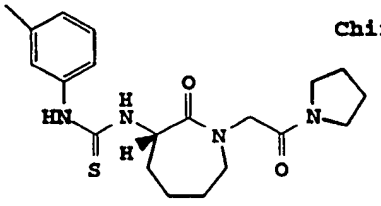

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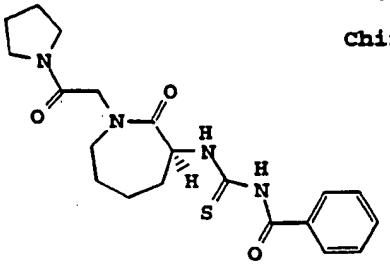

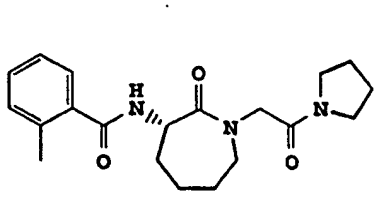

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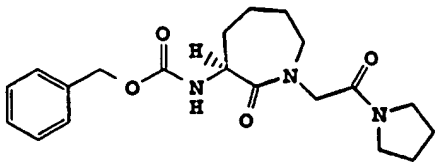

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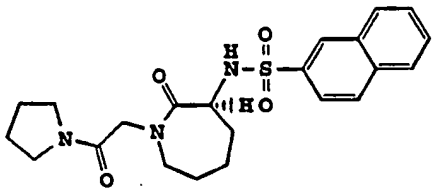

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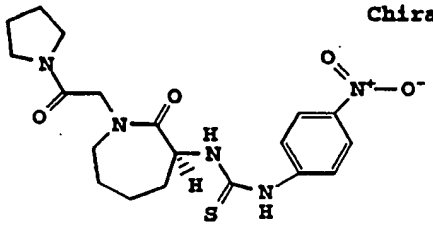

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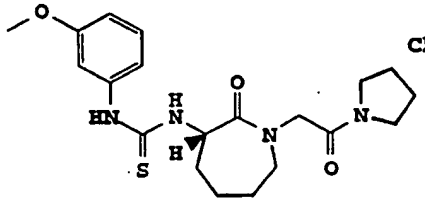

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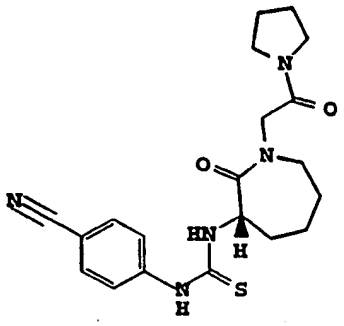

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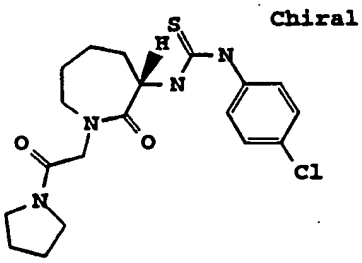

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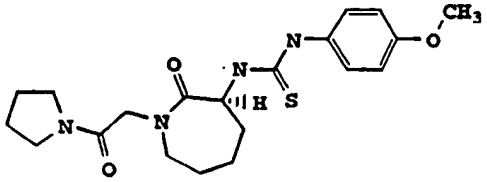

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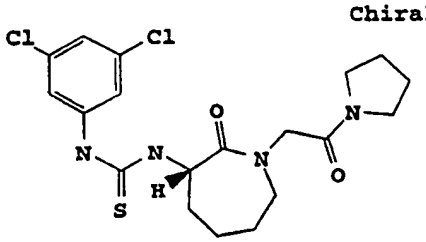

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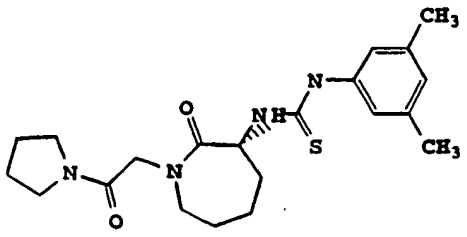

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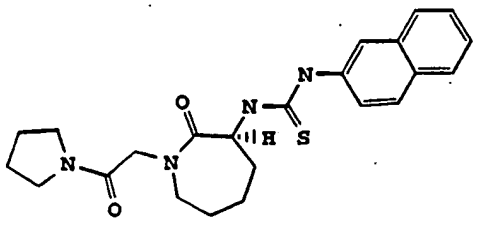

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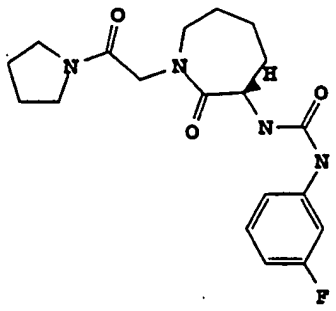

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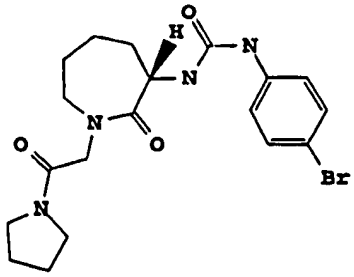

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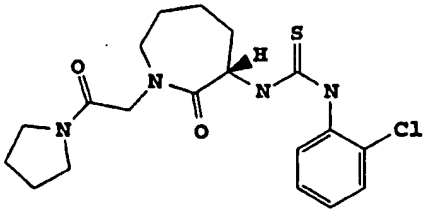

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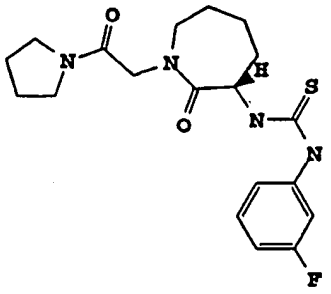

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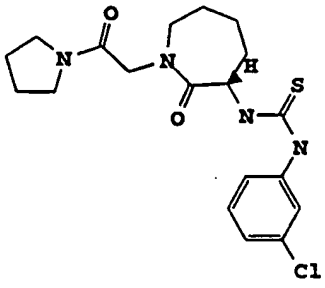

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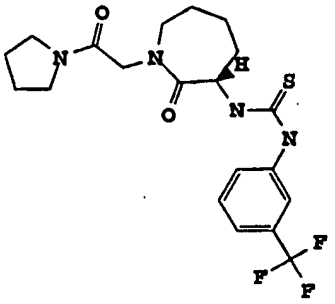

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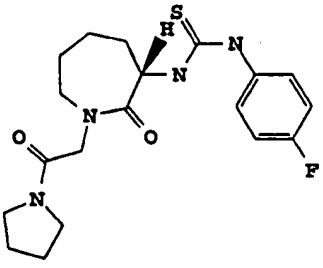

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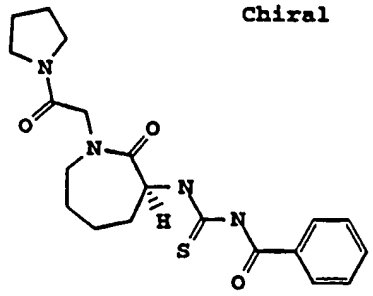

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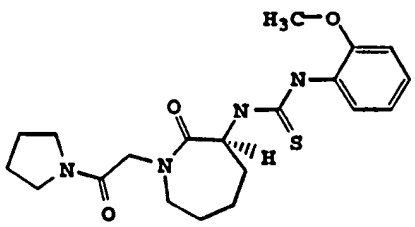

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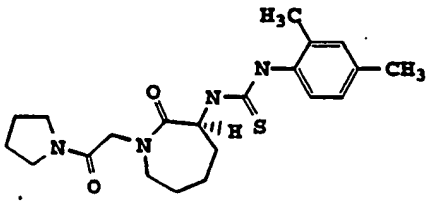

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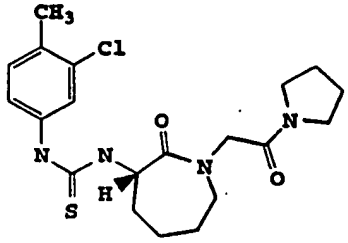

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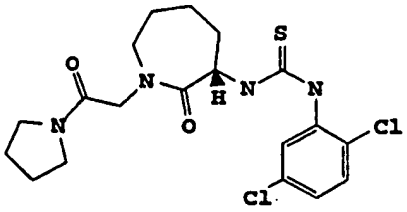

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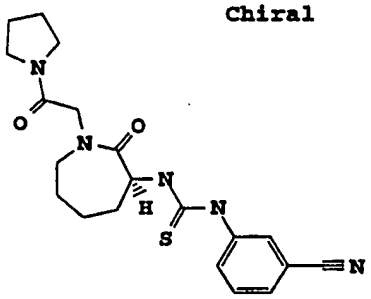

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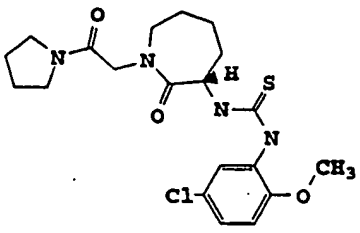

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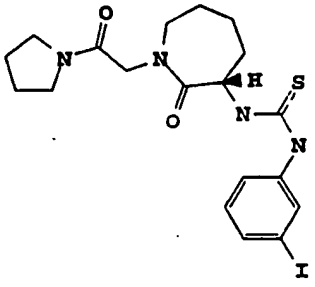

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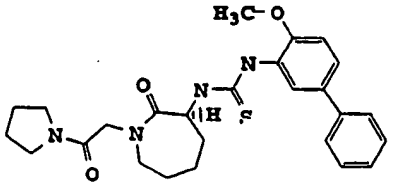

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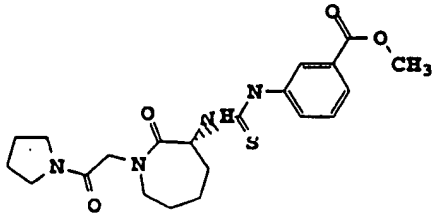

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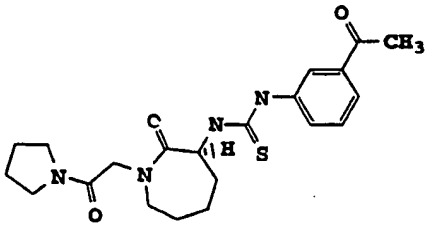

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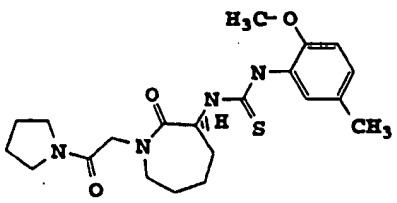

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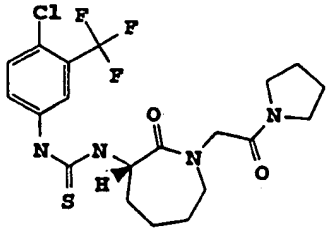

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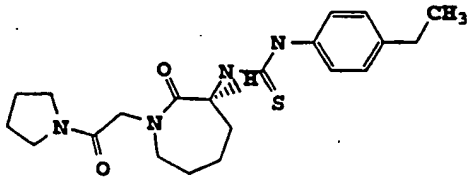

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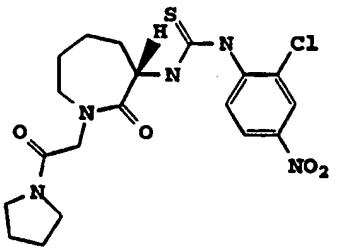

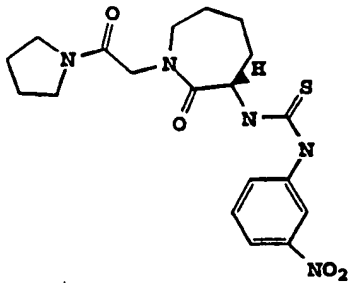

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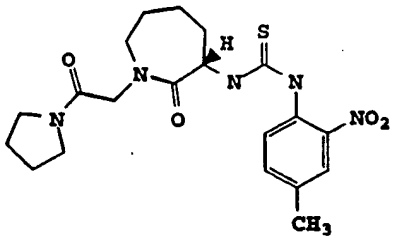

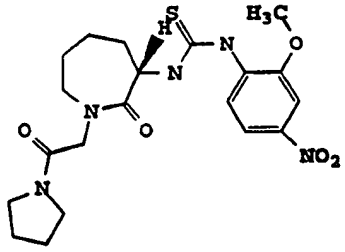

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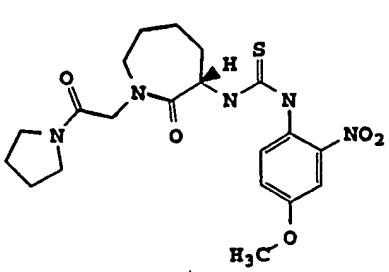

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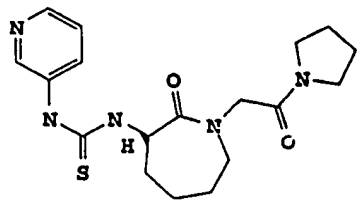
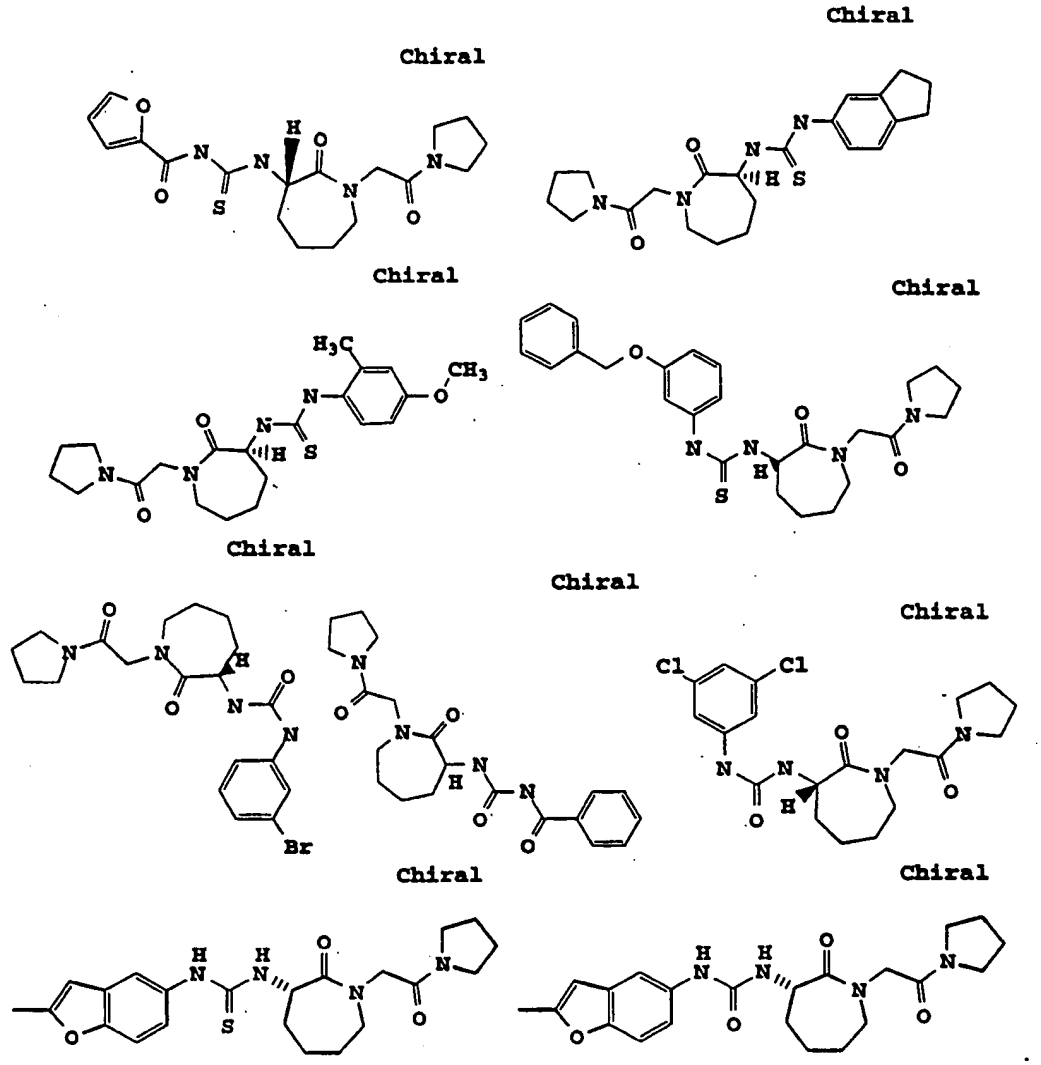
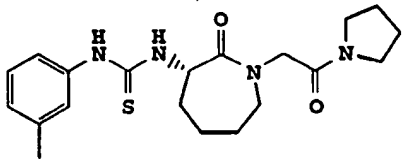




11. The compound as defined in Claim 1 having the structure



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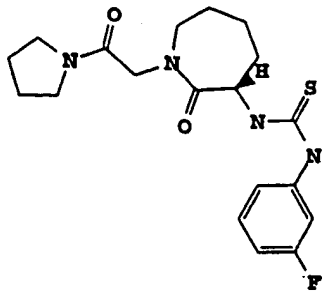

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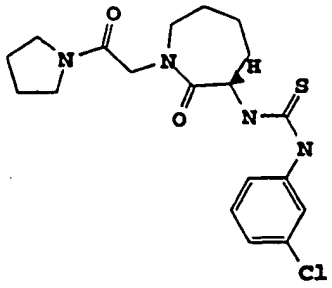

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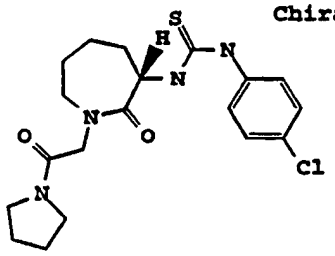

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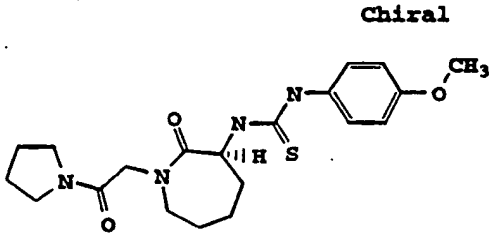

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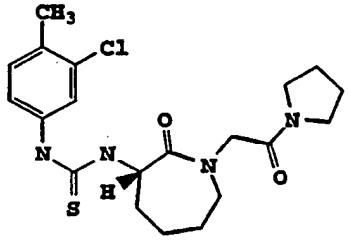

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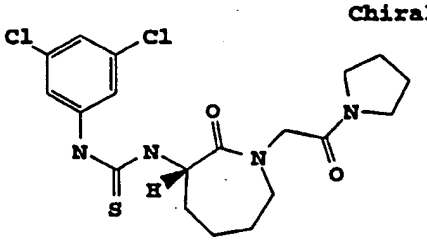

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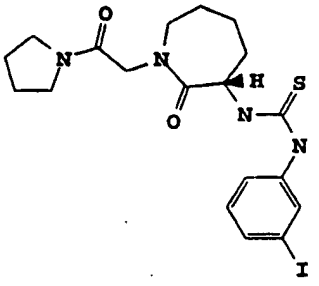

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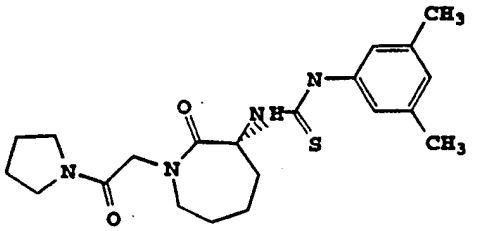

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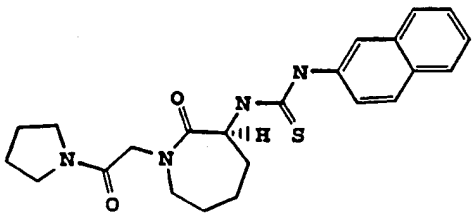
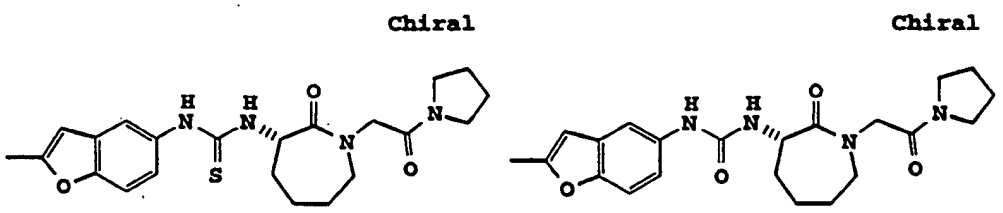
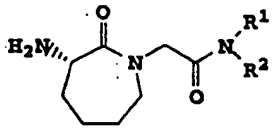


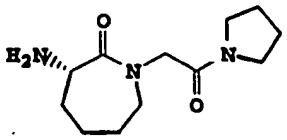


12. A compound having the structure



wherein R^1 and R^2 are the same or different and are independently selected from alkynyl, heteroaryl, heteroarylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, or R^1 and R^2 can be taken with the nitrogen to which they are attached to form a cycloheteroalkyl ring; all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheterolkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, alkylamino, dialkylamino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, alkylsulfinyl; or a pharmaceutically acceptable salt thereof.

13. The compound as defined in Claim 11 having the formula



14. A pharmaceutical composition comprising a compound as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.

15. A method for preventing or treating cardiovascular diseases associated with thromboses, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

16. A method for preventing or treating thromboses, coronary artery disease or cerebrovascular disease, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/01859

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 223/06, 401/02, 403/02; A61K 31/4427, 31/496, 31/55
US CL : 540/524, 527, 528; 514/212.03, 212.08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 540/524, 527, 528; 514/212.03, 212.08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,155,102 (GIANNESSI et al.) 13 October 1992, column 1, lines 6-35	12, 13
—		---
A		1-11, 14-16
A	US 5,672,598 (DE et al.) 30 September 1997	1-16
A	WO 96/11940 (GLAXO) 25 April 1996.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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